BEST AVAILABLE IMAGES

Defective images within this document are accurate representation of The original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/57, 31/165 — A1

(11) International Publication Number: WO 99/00134

(43) International Publication Date: 7 January 1999 (07.01.99)

(21) International Application Number: PCT/SE98/01089

(22) International Filing Date: 8 June 1998 (08.06.98)

(30) Priority Data:
08/883,823 27 June 1997 (27.06.97) US

(71) Applicant: ASTRA AKTIEBOLAG (publ) [SE/SE]; S–151 85 Södertälje (SE).

(72) Inventors: AXELSSON, Bengt; Astra Draco AB, P.O. Box 34, S–221 00 Lund (SE). KÄLLSTRÖM, Leif; Astra Draco AB, P.O. Box 34, S–221 00 Lund (SE). TROFAST, Jan; Astra Draco AB, P.O. Box 34, S–221 00 Lund (SE).

(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S–151 85 Södertälje (SE).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NEW COMBINATION OF ANTIASTHMA MEDICAMENTS

(57) Abstract

The invention provides a composition or kit having as a first active ingredient formoterol, or a salt or solvate derivative thereof, and having as a second active ingredient ropfleponide, or a fatty acid ester thereof. Also disclosed are methods for treating respiratory disorders using this composition or kit.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

NEW COMBINATION OF ANTIASTHMA MEDICAMENTS

Field of the Invention

The present invention relates to compositions and methods useful in the treatment of respiratory disorders, particularly asthma.

Background of the Invention

Despite recent advances in the awareness of asthma and the introduction of powerful and effective anti-asthma drugs, asthma remains a poorly understood and frequently poorly treated disease. There have been recent advances in the treatment of the disease which result from the recognition that asthma is a chronic inflammatory disease. Therapy is now aimed at both controlling the symptoms and reducing the inflammation. The symptoms include uncontrolled airway inflammation which may lead to mucosal damage and structural changes possibly leading to irreversible narrowing of the airways and fibrosis of the lungs.

The symptoms may be controlled by β_2-adrenoreceptor agonists such as salbutamol, bambuterol, clenbuterol, fenoterol, procaterol, bitolterol, broxaterol, salmeterol, terbutaline and formoterol.

Prophylactic therapy is typically provided by steroids such as beclomethasone dipropionate (BDP), beclomethasone monopropionate (BMP), flunisolide, triamcinolone acetonide, dexamethasone, tipredane, ciclesonid, momethasone, RPR 106541, fluticasone or fluticasone propionate and budesonide or by way of sodium cromoglycate or nedocromil sodium.

Summary of the Invention

The invention is based on the discovery that formeterol and rofleponide esters, or their salts or solvates, when administered to a patient either concurrently or sequentially, are unexpectedly effective in treating respiratory disorders involving inflammation, such as asthma. Accordingly, the invention features a composition having, in an admixture: (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate of formoterol, or a solvate of such a salt; and (b) a second active ingredient which is rofleponide or a fatty acid ester of rofleponide.

It is preferred that the molar ratio of (a) to (b) is from 1:1 to 1:100, preferably from 1:1 to 1:60, more preferably from 1:1 to 1:35, and most preferably from 1:16.

The first active ingredient (a) of the composition can be, for example, formoterol fumarate dihydrate, and the second active ingredient (b) of the composition can be, for example, rofleponide palmitate.

The composition can be provided in the form of a dry powder, the particles of which may have a mass median diameter of less than 10μm.

The invention also includes a kit containing: (a) a vessel containing a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; (b) a vessel containing a second active ingredient that is either rofleponide or a fatty acid ester of rofleponide; and (c) instructions for the sequential or simultaneous administration of the first and second active ingredients to a patient in need thereof.

A patient suffering from a respiratory disorder such as asthma can be treated by administering (e.g., via inhalation), simultaneously or sequentially, (a) a dose of a first active ingredient selected from the group consisting of formoterol, a pharmaceutically acceptable salt or solvate thereof, and a solvate of such a salt; and (b) a dose of a second active ingredient selected from the group consisting of rofleponide and a fatty acid ester of rofleponide. The active ingredients can be provided to the patient for inhalation in dry powder form.

When administered sequentially, the active ingredients can be administered in either order, and within a two-hour time period. For example, the first active ingredient can be

administered to the patient less than about 30 minutes after the second active ingredient, or the second active ingredient can be administered to the patient less than about 30 minutes after the first active ingredient.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

The combination according to the invention has the advantage that the toal dose of each active ingredient can be decreased and is more likely to provide patient compliance then would be extected from the properties of the individual active ingredients.

Detailed Description

The invention provides a composition having (a) a first active ingredient selected from the group consisting of formoterol, a pharmaceutically acceptable salt or solvate of formoterol, and a solvate of such a salt; (b) a second active ingredient selected from the group consisting of rofleponide and a fatty acid ester of rofleponide; and, optionally, (c) one or more pharmaceutically acceptable additives, diluents or carriers.

It has been found, using a sephadex-induced edema model (Källström et al., Agents and Action 17:355-377 (1985)), that the combination of active ingredients provides a significantly enhanced anti-inflammatory effect compared to the sum of the individual anti-inflammatory effects of the two active ingredients, thus providing a significant advantage.

The first and second active ingredients of the composition can be administered simultaneously or sequentially to treat respiratory disorders. By simultaneous is meant that the first and second active ingredients (a) and (b) are administered concomitantly, for example as an admixture. Sequential administration generally comprises administering one immediately after the other. They still have the desired effect if they are administered separately but not more than about two hours apart, for example no more than 30 minutes and preferably no more than 5 minutes apart.

Preferably the composition is administered to provide a daily dose of from 0.5 to 200 nmol (preferably from 4 to 100 nmol) of (a) and from 0.5 to
1140 nmol (preferably 14 to 285 nmol and more preferably from 14 to 285 nmol) of (b) (subject to the molar ratio of (a) to (b) being from 1:1 to 1:100).

When (a) is formoterol fumarate dihydrate, the preferred daily dose is from 0.2 to 84 μg (preferably from 2 to 42 μg) of (a), and from 0.4 to 800 μg (preferably from 10 to 400 μg, more preferably from 10 to 200 μg) of (b) where (b) is rofleponide palmitate (subject to the molar ratio of (a) to (b) being within the range of from 1:1 to 1:100).

Suitable physiologically acceptable salts of formoterol include acid addition salts derived from inorganic and organic acids, for example the chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalene-carboxylate or oleate salts or solvates thereof. Active ingredient (a) is preferably formoterol fumarate, especially as the dihydrate.

Rofleponide is preferably esterified by a palmitoyl group.

Preferably each of the active ingredients comprises one or more pharmaceutically acceptable additives, diluents or carriers, more preferably in an amount of from 50 to 2000 μg in a daily dose, most preferably in an amount of from 100 to 1000 μg. Examples of suitable diluents or carriers include lactose, dextran, mannitol and glucose. Preferably lactose is used.

Since active ingredient (b) is preferably a fatty acid ester, formulations containing it are desirably liposomal or proliposomal if they are dry powder formulations. Suitable proliposomal formulations of fatty acid esters of rofleponide are described in WO 96/19199. For improved stability the formulation may comprise tocopherol, especially α-tocopherol.

Active ingredients (a) and (b) may optionally be formulated together to be administered simultaneously. For example, they may be formulated in admixture as a proliposomal powder, for example of the general type described in WO 96/19199 (preferably containing tocopherol as a stabilizing agent) or as an intimate mixture of (a) in the form of a dry powder and a proliposomal dry powder containing (b).

One or more of the active ingredients according to the invention are preferably in the form of a dry powder, more preferably a micronised dry powder, e.g. having a mass median diameter of less than 10μm, for example from 1 to 5μm, most preferably an

agglomerated micronised dry powder. Alternatively active ingredient (a) may be in the form of an ordered mixture with ingredient (c). The ingredients used in the invention can be obtained in these preferred forms using methods known to those of skill in the art.

The invention further provides a method of treating a respiratory disorder, which is preferably asthma, chronic obstructive pulmonary disease (COPD) and/or rhinitis, which method comprises applying to a patient suffering from, or liable to suffer from, such a disorder a therapeutically effective amount of a combination according to the invention.

According to the invention there is further provided the use of an admixture or kit according to the invention in the manufacture of a medicament for simultaneous, separate or sequential use in therapy, preferably in the treatment of a respiratory disorder, e.g. asthma, chronic obstructive pulmonary disease (COPD) and/or rhinitis.

Administration may be by inhalation orally or intranasally. The ingredients are preferably adapted to be administered from a dry powder inhaler.

The combination may optionally be administered as divided doses from 1 to 4, and preferably once or twice a day, which means unit doses from 0.05 μg to 84 μg (preferably from 0.5 μg to 42 μg) of formoterol fumarate dihydrate and from 0.1 μg to 800 μg (preferably from 2.5 μg to 400 μg) of rofleponide palmitate.

Example 1

Rofleponide palmitate (10 parts by weight), dipalmitoylphosphatidylcholine (63 parts), dimyristoylphosphatidylcholine (24 parts), sodium dipalmitoylphosphatidylglycerol (3 parts) and racemic α-tocopherol (0.1 part) were dissolved in tertiary butanol (1300 parts) at 80°C. The solution was poured onto the shelves of a freeze-dryer cooled to -35°C. The solution had reached this temperature after about 30 minutes, the pressure in the freeze-dryer was then reduced in order to induce sublimation of the solvent. While the rate of sublimation could be adjusted by decreasing the pressure and increasing the temperature, the temperature throughtout the process was not allowed to exceed -10°C. Freeze-drying was continued until all the solvent had been removed. The resulting powder was scraped from the shelves of the freeze-dryer and passed through a sieve. This powder was micronised in an air jet mill to a powder particle size of less than 5 μm.

0.5 parts of formoterol fumarate dihydrate was mixed with 79.5 parts of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. This mixture (80 parts) was added to the steroid/lipid powder mixture (20 parts) by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into a blister, a capsule or a storage chamber of an inhaler for use in a dry powder inhaler.

Other Embodiments

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A therapeutic composition comprising, in admixture:

(a) a first active ingredient selected from the group consisting of formoterol, a pharmaceutically acceptable salt or solvate thereof, and a solvate of such a salt; and

(b) a second active ingredient selected from the group consisting of rofleponide and a fatty acid ester of rofleponide.

2. The composition of claim 1, wherein the molar ratio of (a) to (b) in the composition is from 1:1 to 1:100.

3. The composition of claim 1 or 2, wherein (a) is formoterol fumarate dihydrate.

4. The composition of any one of claims 1 to 3, wherein (b) is rofleponide palmitate.

5. The composition of any one of claims 1 to 4, additionally comprising a pharmaceutically acceptable additive, diluent or carrier suitable for inhalation.

6. The composition of any one of claims 1 to 5, in the form of a dry powder the particles of which have a mass median diameter of less than 10μm.

7. A kit comprising

(a) a vessel containing a first active ingredient selected from the group consisting of formoterol, a pharmaceutically acceptable salt or solvate thereof, and a solvate of such a salt;

(b) a vessel containing a second active ingredient selected from the group consisting of rofleponide and a fatty acid ester of rofleponide; and

(c) instructions for the sequential or simultaneous administration of the first and second active ingredients to a patient in need thereof.

8. The kit of claim 7, wherein the first active ingredient is formoterol fumarate dihydrate.

9. The kit of claim 7 or 8, wherein the second active ingredient is rofleponide palmitate.

10. The kit of any one of claims 7 to 9, wherein the instructions specify that the first and second active ingredients be administered in a molar ratio ranging from 1:1 to 1:100.

11. A method of treating a respiratory disorder, which method comprises simultaneously or sequentially administering to a patient suffering from the disorder

(a) a dose of a first active ingredient selected from the group consisting of formoterol, a pharmaceutically acceptable salt or solvate thereof, and a solvate of such a salt; and

(b) a dose of a second active ingredient selected from the group consisting of rofleponide and a fatty acid ester of rofleponide.

12. The method of claim 11, wherein the molar ratio of (a) to (b) is from 1:1 to 1:100.

13. The method of claim 11 or 12, wherein the first active ingredient is formoterol fumarate dihydrate.

14. The method of any one of claims 11 to 13, wherein the second active ingredient is rofleponide palmitate.

15. The method of any one of claims 11 to 14, wherein the first active ingredient is administered to the patient less than about 30 minutes before and after the second active ingredient.

16. The method of any one of claims 11 to 15, wherein the doses are administered to the patient by causing the patient to inhale them simultaneously.

17. The method of claim 16, wherein the first and second active ingredients are both provided to the patient for inhalation in dry powder form.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01089

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/57, A61K 31/165
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9619199 A1 (ASTRA AKTIEBOLAG), 27 June 1996 (27.06.96), page 5, line 20 - page 6, line 21, the claims	1-17
X	WO 9311773 A1 (AKTIEBOLAGET ASTRA), 24 June 1993 (24.06.93), page 3, line 19 - page 4, line 34, the claims	1-17
P,X	WO 9815280 A1 (ASTRA AKTIEBOLAG), 16 April 1998 (16.04.98)	1-17
A	WO 9632095 A1 (ASTRA AKTIEBOLAG), 17 October 1996 (17.10.96), page 5, line 9 - line 16, the claims	1-17

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 Sept 1998	28 -09- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01089

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9505805 A1 (ASTRA AKTIEBOLAG), 2 March 1995 (02.03.95), page 7, line 1 - page 8, line 18, the claims -- --------	1-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01089

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11-17
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 11-17 relate to a method of treatment of the human or animal body by surgery or by therapy. See PCT, Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged efects of the compounds/compositions.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/07/98

International application No.
PCT/SE 98/01089

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9619199 A1	27/06/96	AU 693632 B	02/07/98
		AU 4360596 A	10/07/96
		CA 2208517 A	27/06/96
		CN 1171047 A	21/01/98
		CZ 9701948 A	15/10/97
		EP 0800383 A	15/10/97
		FI 972653 A	20/08/97
		HU 77628 A	29/06/98
		IL 116454 D	00/00/00
		NO 972847 A	19/06/97
		PL 320825 A	10/11/97
		SE 9404466 D	00/00/00
		SK 81497 A	05/11/97
		ZA 9510751 A	24/06/96
		SE 9502369 D	00/00/00
WO 9311773 A1	24/06/93	AU 673660 B	21/11/96
		AU 3085892 A	19/07/93
		CA 2123909 A	24/06/93
		CZ 9401434 A	15/12/94
		EP 0613371 A	07/09/94
		HR 921445 A	31/12/94
		HU 75156 A	28/04/97
		HU 9401843 D	00/00/00
		JP 7502036 T	02/03/95
		NO 942116 A	07/06/94
		NZ 246050 A	21/12/95
		SG 48301 A	17/04/98
		SK 73394 A	08/03/95
		US 5674860 A	07/10/97
WO 9815280 A1	16/04/98	AU 4578297 A	05/05/98
		SE 9603669 D	00/00/00
WO 9632095 A1	17/10/96	AU 694863 B	30/07/98
		AU 5352496 A	30/10/96
		CA 2217062 A	17/10/96
		CN 1186428 A	01/07/98
		EP 0795150 A	17/09/97
		EP 0820276 A	28/01/98
		IL 117841 D	00/00/00
		NO 974557 A	02/10/97
		SE 9501384 D	00/00/00

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/07/98

International application No.
PCT/SE 98/01089

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9505805 A1	02/03/95	AU 681186 B	21/08/97
		AU 7626494 A	21/03/95
		BR 9407320 A	16/04/96
		CN 1133004 A	09/10/96
		CZ 9600544 A	15/05/96
		EP 0717616 A	26/06/96
		FI 960869 A	26/02/96
		HU 74000 A	28/10/96
		HU 9600447 D	00/00/00
		IL 110698 D	00/00/00
		JP 9501930 T	25/02/97
		NO 960744 A	23/02/96
		NZ 273090 A	24/06/97
		PL 313142 A	10/06/96
		SE 9302777 D	00/00/00
		SG 47760 A	17/04/98
		SK 23496 A	05/02/97
		US 5637620 A	10/06/97
		US 5709884 A	20/01/98
		ZA 9405675 A	29/04/96